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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/057,288	LARSEN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,9,10,12,13,30,33,34,36,37,44-52,54-60 and 62-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 5-6, 9-10, 12-13, 30, 33-34, 36-37, 44-52, 54-60 and 62-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the Appeal Brief filed on 12/28/2007, PROSECUTION IS HEREBY REOPENED. New Grounds of Rejections are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below.

2. Claims 1-2, 5-6, 9-10, 12-13, 30, 33-34, 36-37, 44-52, 54-60 and 62-74 are pending.

Claims 3-4, 7-8, 11, 14-17, 18-29, 31-32, 35, 38-43, 53 and 61 have been canceled previously.

3. As indicated previously, applicant's election of the following species:
the alkylating agent is busulfan;
the first ligand is a soluble CTLA4;
the second ligand is anti-CD40 antibody; and
the targeted condition is solid organ or tissue/cellular transplant
with traverse has been acknowledged.

As indicated previously, given amending the claims to provide the alkylating agent / busulfan after the administration of bone marrow derived stem cells,
the search has been extended to another alkylating agent (i.e. cyclophosphamide) in view of the enablement issues under 35 USC 112, first paragraph, indicated herein for "administering the elected alkylating agent busulfan after the administration of bone marrow cells / stem cells" indicated below and in the interest of compact prosecution.

Claims 1-6, 9-13, 17, 28-37 and 44-52 and 54-60 and 62-74 are being examined to the extent that they read on the elected species (e.g. busulfan as well as cyclophosphamide, the first ligand is a soluble CTLA4, the second ligand is anti-CD40 antibody and the targeted condition is solid organ or tissue/cellular transplant) for examination purposes in the instant application.

Applicant's amendment, filed 12/18/06, acknowledges the species election.

4. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

This Office Action will be in response to applicant's arguments, filed in applicant's Appeal Brief, filed 12/28/07.

The rejections of record can be found in the previous Office Actions.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

See the previous Office Actions for a more complete analysis of the rejections of record.

New Grounds of Rejection have been set forth herein to provide for a clearer support for two key aspects of the claimed invention that applicant has asserted distinguishes the claimed invention from the prior art.

The key to applicant's assertions is that the claimed invention provides methods for inhibiting or reducing rejection of a solid organ or tissue/cellular transplant in a subject comprising the **following sequence of steps**: administering T cell depleted bone marrow cells to the subject before, during or after the solid organ or tissue/cellular transplant; administering an alkylating agent (e.g., busulfan) to the subject in an amount that facilitates mixed chimerism; administering a subsequent dose of T cell depleted bone marrow; and administering an immunosuppressive composition that blocks T cell costimulatory signals in the subject before, during or after the transplant.

In particular, applicant's assertions focus on the position that Sykes does not teach any therapeutic sequence and that the claimed method requires:

administration of T cell depleted bone marrow to a subject;

administration of an alkylating agent **after** the T cell depleted bone marrow to a subject;

administration of additional T cell depleted bone marrow after the alkylating agent to a subject; and

administering an immunosuppressive composition that blocks T cell costimulatory signals in the subject.

Additional references are provided to clarify the prior art of record to address the *administration of an alkylating agent **after** the T cell depleted bone marrow to a subject;* which appears to be central to applicant's arguments.

5. The filing date of the instant claims is deemed to be the filing date of priority application USSN 60/303,142, filed 07/05/2001.

Applicant's assertions, filed 12/18/06, concerning the priority of the instant claims have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal concerning the priority of the instant claims are essentially the same of record and reiterated herein for applicant's convenience.

In contrast to applicant's continual reliance and assertions of inferring "limitations" , the disclosure of experimental observations concerning the ability of a single dose of busulfan prior to the transplantation (i.e. intravenous infusion) of T cell-depleted bone marrow cells (e.g. comprising hemopoietic stem cells) in priority USSN 60/264,528, filed 1/26/05;

does not provide sufficient written description for

(a) "administering TDBM before, during and/or after a solid organ or tissue/cellular transplant";

(b) "subsequently administering an alkylating agent wherein the alkylating agent is selected from a group consisting of alkylsulfonates, nitrogen mustards, oxazaposporines, nitrosoureas, (including busulfan)"; or

(c) "administering an costimulatory blockade before, during and/or after a solid organ or tissue/cellular transplant blockade which costimulatory blockade comprises a combination of a first ligand that interferes with binding of CD28 to either CD80 or CD86, and a second ligand that interferes with binding of CD154 to CD40"; as currently claimed.

Further, the priority application USSN 60/264,528, filed 1/26/01 does not appear to provide sufficient written support for

all of the claimed dosage amounts and administration timing (e.g., see claims 30, 57-60, 62-63);

all of the claimed characteristics of the claimed soluble CTLA4 molecule (e.g., see claims 44-50, 65-, 73-74);

all of the claimed akylating agents (e.g., see claims 63-64) nor

all of the claimed ligands for CD40 (e.g., see claims 52 and 54-55)

currently recited in the instant application.

These instant claims encompass limitations that represent a departure from the priority USSN 60/264,528, filed1/26/05.

For example, applicant's continual reliance on a limited disclosure and possibly a single or limited species (e.g. busulfan) under certain defined conditions do/does not provide sufficient direction and guidance to the written description of the currently claimed "limitations" "wherein the alkylating agent is selected from a group consisting of alkylsulfonates, nitrogen mustards, oxazaposporines, nitrosoureas" as well as all of the currently claimed dosage amounts and administration timing.

Further, priority application USSN 60/264,528, filed 1/26/01, provides for CTLA4-Ig (versus generic "first ligand that interferes with binding of CD28 to either CD40 or CD86 or the currently claimed CTLA4 modified / mutant molecules) and the anti-CD40L monoclonal antibody only (versus generic "second ligand that interferes with binding of CD154 to CD40).

It is noted that a generic or a sub-generic disclosure cannot support a species unless the species is specifically described. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Therefore, as indicated previously, priority application USSN 60/264,528, filed 1/26/01 does not appear to support the instant claims encompassing methods of inhibiting rejection of a solid organ or tissue/cellular transplant by administering an alkylating agent wherein the alkylating agent is selected from a group consisting of alkylsulfonates, nitrogen mustards, oxazaposporines, nitrosoureas (versus experimental conditions using bulsufan only) and subsequently administering cell depleted bone marrow cells before, during or after as the transplant, as well as administering CD28 / CD80 / CD86 / CD154 / CD40 inhibitors.

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Therefore, the filing date of the instant claims is still deemed to be the filing date of priority application USSN 60/303,142, filed 07/05/2001.

If applicant desires priority prior to 07/05/2001; applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earliest priority application asserted.

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Applicant's arguments filed 12/28/2007 in the appeal Brief have been fully considered but have not been found convincing essentially for the reasons of record.

6. Upon reconsideration of applicant assurances for the deposit of the biological matierals deposited as ATCC Numbers 68629 and 10762 in the Appeal Brief, filed 12/28/2008; the previous rejection under 35 U.S.C. 112, first paragraph, enablement for the deposit of biological materials has been withdrawn.

7. Enablement

Claims 47-50 and 73-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific mutant CTLA4 molecules such as the L104EA29YIg molecule disclosed in the specification as filed or claimed (e.g. see Example 8 on pages 67-83 of the instant specification),
does not reasonably provide enablement for any "CTLA4 mutant molecule" to be employed as an immunosuppressive agent in the instant claimed methods.
The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's assertions, filed 12/28/2007, concerning the priority of the instant claims have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments filed 12/28/2007 in the Appeal Brief and the examiner's rebuttal concerning the breadth of "soluble CTLA4 mutant molecules" of the instant claims are essentially the same of record and reiterated herein for applicant's convenience.

However, it is noted that the claims now include claims 47-50 and 73-74, given that it does not appear that these claims recite specific mutant CTLA4 molecules.

Applicant's arguments have not been found persuasive.

The following is reiterated for applicant's convenience.

Applicant's continual reliance upon amending the claims to recite "soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86" and examples of certain CTLA4 mutant molecules is acknowledged.

However, the claims relies upon a generic recitation of "a soluble CTLA4 mutant" together with a function but in the absence of a those structures or elements of CTLA4 mutant that are important or critical to a "soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86.

For example, it appears that applicant relies upon the disclosure of U.S. Patent No. 5,773,253; yet the patented claims are still limited in structure as well as function.

Again as pointed out previously, applicant has acknowledged that CTLA4 mutant molecule means wildtype CTLA4 as shown in Figure 19 or any portion or derivative thereof, that has a mutation or multiple mutations and submits Examples of six CTLA4 mutant molecules are provided.

Also, applicant has relied upon disclosing a number of different assays for the identification of CTLA4 mutant molecules as claimed.

However, such assays without more precise guidelines amount to little more that a starting point, a direction for further research. The specification provides for a plan or an invitation for those of skill in the art to experiment practicing the claimed invention but does not provide sufficient guidance or specificity as to how to execute that plan. It provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention, but this is not adequate to constitute enablement in that will enable any person skilled in the art to make and use the invention for any mutant CTLA4 molecule including any mutation or mutations as well as any derivative of CTLA4 as broadly encompassed by the claimed invention. At most, its description will enable a person of skill in the art to attempt to discover how to practice the claimed invention, which is not enough.

Also, the following previously of record is provided for applicant's convenience.

Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies any "CTLA4 mutant molecule" that inhibits graft rejection encompassed by the claimed methods. "CTLA4 mutant molecule" may have some notion of the source of the "first ligand that interferes with binding of CD28 to either CD80 or CD86", however, claiming biochemical molecules by a particular name and a modification of said molecule (e.g. "CTLA4 mutant molecule") by applicant fails to distinctly claim what that "CTLA4 mutant molecule" is and what it is made up of or how it differs from native CTLA4. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable any "CTLA4 mutant molecule".

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus of "CTLA4 mutant molecules". The instant invention encompasses any "CTLA4 mutant molecule", yet the instant specification does not provide sufficient guidance and direction as to the selection of particular sequences essential for the unrecited (claim 47) and recited function (see claim 48), which interferes with binding of CD28 to either CD80 or CD86 in the inhibition of graft rejection.

Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g., ligand or receptor) requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which a polypeptide's structure relates to its functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects ligands and receptors and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Because of the lack of sufficient guidance and predictability in determining which structures would lead to "CTLA4 mutant molecules" other than the CTLA4 mutant molecules disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of ligand and receptors encompassed by the claimed invention.

Attwood (Science 290: 471–473, 2000) notes in the Introductory paragraphs that it is presumptuous to make functional assignments merely on the basis of some degrees of similarity between sequences (and it is not always clear what we mean by "function"); very few structures are known compared with the number of sequences, and structure prediction methods are unreliable (and knowing structure does not inherently tell us functions").

Skolnick et al. (Trends in Biotechnology 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

This requirement is emphasized in the instant example since, as summarized in Figures 2 and 3 of Coyle et al. (Nature Immunology 2: 203-209, 2001) the B7-like family members have distinct expression patterns and distinct functions.

Metzler et al. (Nature Structural Biology 4: 527- 531, 1997) describe various CTLA4 mutants and their varying effects on CD80 and CD86 binding (see entire document, including Table 2 on page 530). Here, there does not appear sufficient predictability as to those mutations that result in a particular function, as the mutations had multiple effects on said CD80 and CD86 binding, including little or no effects.

Thus, the experimentation left to those skilled in the art to determine the function of the scope of "CTLA4 mutant molecules" that interfere with binding of CD28 to either CD80 and CD86 and inhibit graft rejection encompassed by the claimed invention is unnecessarily and improperly extensive and undue.

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus of "CTLA4 mutant molecules". It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biology, expression and pharmacology of receptors and ligands.

In the absence of sufficient guidance and direction to the structural and functional analysis, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue to make and use "CTLA4 mutant molecules" other than those specific "CTLA mutant molecules" which interfere with the binding of CD28 to either CD80 or CD86 as disclosed in the specification as filed (or as recited in claims 49-50) as the first ligand in the claimed methods to inhibit graft rejection.

Again, applicant is invited to limit the claims to those "CTLA4 mutant molecules" with the appropriate inhibitory properties disclosed in the specification as filed as the first ligand in the claimed methods.

8. **New Grounds of Rejection**.
This is a written description / not a new matter rejection.

Claims 47-50 and 73-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims recite and encompass "a soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86" in the absence of a those structures or elements of CTLA4 mutant that are important or critical to a "soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86.

As noted in the enablement rejection of record, it appears that applicant relies upon the disclosure of U.S. Patent No. 5,773,253; yet the patented claims are still limited in structure as well as function.

As noted in the enablement rejection of record, applicant has acknowledged that CTLA4 mutant molecule means wildtype CTLA4 as shown in Figure 19 or any portion or derivative thereof, that has a mutation or multiple mutations and submits Examples of six CTLA4 mutant molecules are provided.

Also, applicant has relied upon disclosing a number of different assays for the identification of CTLA4 mutant molecules as claimed.

The recitation of "a soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86" does not meet the written description provision of 35 USC 112, first paragraph.

There is insufficient guidance and direction as to the written description of the claimed "soluble CTLA4 mutant molecule that interferes with the binding of CD28 to CD80 and/or CD86".

Because of the lack of sufficient guidance in determining which structures would lead to "CTLA4 mutant molecules" other than the CTLA4 mutant molecules disclosed in the specification as filed with the desired properties and that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.);
one of skill in the art would conclude that applicant was not in possession of the structural attributes of a representative number of species possessed by the members of the genera of "soluble CTLA4 mutant molecules", broadly encompassed by the claimed invention.

Attwood (Science 290: 471–473, 2000) notes in the Introductory paragraphs that it is presumptuous to make functional assignments merely on the basis of some degrees of similarity between sequences (and it is not always clear what we mean by "function"); very few structures are known compared with the number of sequences, and structure prediction methods are unreliable (and knowing structure does not inherently tell us functions").

Skolnick et al. (Trends in Biotechnology 18: 34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

This requirement is emphasized in the instant example since, as summarized in Figures 2 and 3 of Coyle et al. (Nature Immunology 2: 203-209, 2001) the B7-like family members have distinct expression patterns and distinct functions.

Metzler et al. (Nature Structural Biology 4: 527- 531, 1997) describe various CTLA4 mutants and their varying effects on CD80 and CD86 binding (see entire document, including Table 2 on page 530). Here, there does not appear sufficient predictability as to those mutations that result in a particular function, as the mutations had multiple effects on said CD80 and CD86 binding, including little or no effects.

The instant application has not provided a sufficient description showing possession of the necessary functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genera of "soluble CTLA4 mutant molecules", broadly encompassed by the claimed invention.

Further, the Court has interpreted 35 U.S.C. §112, first paragraph, to require the patent specification to "describe the claimed invention so that one skilled in the art can recognize what is claimed. Enzo Biochem, Inc. v. Gen-Probe Inc, 63 USPQ2d 1609 and 1618 (Fed. Cir. 2002). In evaluating whether a patentee has fulfilled this requirement, our standard is that the patent's "disclosure must allow one skilled in the art 'to visualize or recognize the identity of' the subject matter purportedly described." Id. (quoting Regents of Univ. of Cal. v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed Cir. 1997)).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483.

The Court has held that the disclosure of screening assays and general classes of compounds was not adequate to describe compounds having the desired activity: without disclosure of which peptides, polynucleotides, or small organic molecules have the desired characteristic, the claims failed to meet the description requirement of § 112. See University of Rochester v. G.D. Searle & Co., Inc., 69 USPQ2d 1886,1895 (Fed. Cir. 2004).

The problem here is that the instant specification fails to provide a disclosure of which residues are required for the "soluble CTLA4 mutant molecule" "to interfere with the binding of CD28 to CD80 and/or CD86", broadly encompassed by the claimed invention.

A skilled artisan cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus that exhibit this functional property.

Therefore, there is insufficient written description for genera of "soluble CTLA4 mutant molecule" "to interfere with the binding of CD28 to CD80 and/or CD86", broadly encompassed by the claimed invention at the time the invention was made and as disclosed in the specification as filed under the written description provision of 35 USC 112, first paragraph.

Applicant has been reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant is directed to Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday January 2001.

9. **New Grounds of Rejection**.

Additional references are provided to clarify the prior art of record to address the *administration of an alkylating agent **after** the T cell depleted bone marrow to a subject and to address the asserted unexpected advantages of the claimed methods;*
which appears to be central to applicant's arguments.

Claims 1-6, 9-13, 17, 30, 33-37, 44-52, 54-63 and newly submitted claim 64 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513) in view of art known practice and modes of administration of alkylating agents

such as bulsulfan / cyclophosphamide at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. Therapeutic Drug Monitoring 20: 543-549, 1998) and Hassan et al. (Blood 84: 2144-2150, 1994) , The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide) and Shichi et al. (U.S. Patent No. 4,843,092), Strom et al. (in Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, 1996; see pages 451-456), Sykes et al. (Nature Medicine 3: 783-787, 1997) and Wekerle et al. (J. Exp. Med. 187: 2037-2044, 1998) for the reasons of record

and in further view of

Reinherz et al. (U.S. Patent No. 4,443,427), Tomita et al. (J. Immunol. 164: 34-41, 2000) (1449; Exhibit #274), Bingaman et al., Transplantation 69: 2491-2496 (2000) (1449; Exhibit 193), Larsen et al., Current Opinion in Immunology 9: 641-647 (1449; Exhibit 188), and Schaub et al., Journal of Allergy and Clinical Immunology 99: 5206, Abstract 843 (1997) (1449; #264).

Given the broadest reasonable interpretation of the claimed methods that administering an alkylating agent subsequently after administering T cell depleted bone marrow, the following is noted.

Reinherz et al.

Reinherz et al. teach the use of busulfan and immunosuppressives such as cytoxan (i.e., cyclophosphamide) when reconstitution failed (e.g., see column 7, paragraph 3).

Therefore, Reinherz et al. teach the use of busulfan and cyclophosphamide in a conditioning regimen subsequent to previous attempts to transplant bone marrow and in turn, support the obviousness of record in the use of busulfan and cyclophosphamide subsequent to bone marrow transplantation in circumstances wherein additional bone marrow transplantation occurs or is desirable.

Given the broadest reasonable interpretation of the claimed methods that administering an alkylating agent subsequently after administering T cell depleted bone marrow,

Reinherz et al. provides additional evidence to the record, particularly the multiple infusions taught by Sykes et al., that the claimed methods encompass providing busulfan and/or cyclophosphamide subsequently to T cell depleted bone marrow, subsequent to previous attempts to transplant bone marrow.

The claimed methods do not recite a specific temporal element that excludes multiple infusions or attempts to transplant bone marrow and multiple conditioning regimens, including the use of bulsulfan and/or cyclophosphamide.

Tomita et al.

In addition, given the broadest reasonable interpretation of the claimed methods that administering an alkylating agent subsequently after administering T cell depleted bone marrow, Tomita et al. provides for administering busulfan and cyclophosphamide the same day as spleen cells, which provides for the obviousness of providing said alkylating agents subsequent to administering bone marrow, given the use of aklylating agents after administering hemopoietic cells had advantages when given at the same or nearly the same time.

The claimed methods do not recite a specific temporal time frame other than "after". Therefore, when alkylating agents and hemopoietic cells are given the same day, it would have been obvious that one could be given prior to the other or vice versa and not necessarily at exactly the same time or in the same infusion.

Tomita et al. teach regimens incorporating cyclophosphamide and busulfan along with T cell-depleted bone marrow cells for the induction of mixed chimerism and skin allograft tolerance (see entire document, including Abstract, Results and Discussion)

Also, note that more consistent stable mixed chimerism was achieved by the addition of busulfan on day three (day 3) to the spleen cells and cyclophosphamide Groups (e.g., Groups 10 and 11), Wherein it is noted that days two and three (days 2 and 3) are the days of the administration of T cell depleted bone marrow (see Results, particularly page 36, column 2 in *Induction of long-lasting mixed chimeric and skin allograft prolongation by the additional myelosuppresssive treatments*).

In contrast to applicant's assertions of unexpected advantages, the following is noted.

Bingaman et al. teach methods of transplantation of bone marrow in the form of a bone graft to facilitate hemopoietic chimerism and long-term donor-specific hyporesponsiveness (e.g., skin grafts) in the absence of cytoreductive conditioning regimen by employing combined blockade of the CD40 and CD28 costimulatory pathways (See entire document, including Abstract and Discussion).

Larsen et al. teach the advantages and extreme potent inhibition of the simultaneous blockade of the CD40-CD40 and B7-CD28 pathways to inhibit allograft rejection and its applicability to transplantation tolerance clinically (see entire document, including Strategies to induce graft acceptance or tolerance by manipulating CD40 and Conclusions on pages 644-645).

Schaub et al. teach the synergistic effect of blocking, including sequential blockade, of the CD28/B7 and CD40L/CD40 costimulatory pathways in the treatment of autoimmune responses (see Abstract).

Therefore, in contrast to applicant's assertions of unexpected advantages, the additional references of Bingaman et al. and Tomita et al. teach the advantages of mixed chimerism in combination therapy to induce long-term antigen-specific unresponsivness and the additional references of Bingaman et al., Larsen et al. and Schaub et al. teach the advantages, including synergistic effects, of combining blocking both the CD28/B7 and CD40L/CD40 costimulatory pathways in achieving long-term antigen-specific unresponsiveness.

With respect to applicant's assertions filed 12/28/2007 in the Appeal Brief concerning the obviousness of the instant claims have been fully considered but have not been found convincing essentially for the reasons of record.

In addition to the newly added references above, applicant's arguments and the examiner's rebuttal concerning the obviousness of the instant claims are essentially the same of record and reiterated herein for applicant's convenience.

Applicant's arguments have not been found persuasive.

The following of record is reiterated for applicant's convenience.

As indicated previously, with respect to applicant's assertions concerning the newly added Strom et al. (in Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, 1996; see pages 451-456), Sykes et al. (Nature Medicine 3: 783-787, 1997) and Wekerle et al. (J. Exp. Med. 187: 2037-2044, 1998) to the previous rejection of record, the following is noted.

With respect to Strom et al., Sykes et al. and Wekerle et al, applicant asserts that these references fail to teach the use of busulfan in the claimed methods for facilitating mixed hemopoietic chimerism and tolerance induction.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather merely asserts that these prior art references fail to teach and, do not provide sufficient suggestion or motivation to use busulfan in the claimed methods for facilitating mixed hemopoietic chimerism and tolerance induction and does not address the teachings of the references individually and not their teachings individually or in combination.

One cannot show non-obviousness by merely asserting that the references do not provide the sufficient elements of obviousness or by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

These previously newly added references were provided to make it clear that the prior art recognized the combination of immunosuppressive therapies addressing different targets to increase the desired immunosuppressive effect and to decrease the toxicity of each immunosuppressive in such regimens rather than an explicit teaching of using busulfan in the claimed methods for facilitating mixed hemopoietic chimerism and tolerance induction.

Strom et al. teach that it was known and practiced by the ordinary artisan to employ a multitiered approach to immunosuppressive therapy similar in principle to that used in chemotherapy, several agents are used simultaneously, each of which is directed to a different molecular target with the allograft response. Additive-synergistic effects are achieved through application of each agent at relatively low dose, thereby limiting the toxicity of each individual agent while increasing the total immunosuppressive effect (see entire document, including the introduction on page 451).

Sykes et al. also teach the advantages of mixed chimerism in employing immunosuppressive regimens associated with hemopoietic cell transplantation in the induction of central T cell tolerance for clinical use (see entire document, including Abstract and the last paragraph on page 786).

Wekerle et al. also teach the advantages of employing inhibitors of costimulation and CD40:CD40 ligand interactions that lead to chimerism in approaches to induce tolerance and overcome the problems of chronic organ graft rejection and immunosuppression-related toxicity (See entire document, including Abstract, Introduction and Discussion).

Again, in contrast to applicant's assertions of insufficient teachings in the prior art or unexpected advantages, the prior art provides for the combination therapy encompassed by the claimed methods for the same or nearly the same reasons, that is, to achieve long term graft survival and reducing immunosuppression-related toxicities by combining inhibitors of B7:CD28:CTLA4 and CD40:CD40L pathways with standard or current immunosuppression regimens at the time the invention was made with an expectation of success in achieving said goals.

Applicant's continual assertions in the absence of objective evidence to the contrary that the teaching of Sykes that busulfan may be used in lieu of irradiation to create hemopoietic space runs contrary to the clear teaching of the prior art or what was known and practiced for decades by the ordinary artisan.

Also, as previously noted, Hassan et al. clearly states:
"Busulfan has been introduced as an alternative for total body irradiation (TBI). The therapeutic efficacy for busulfan / cyclophosphamide is considered to be equivalent if not superior to cyclophosphamide and TBI."
See page 2144, column 1 of Hassan et al. (Blood 84: 2144-2150, 1994).

Also, as indicated by the various citations of record, busulfan was commonly used in combination with other immunosuppressive regimens in therapeutic regimens of hemopoietic / bone marrow transplantation by the ordinary artisan at the time the invention was made. See the prior art of record, including the background or introductory information provided by Hassan et al. Slattery et al. as well as Sykes et al. and the Andersson et al. U.S. Patent Nos. 5,430,057 and 5,559,148.

Therefore, applicant's continual assertions that busulfan or other alkylating agents were not employed in transplantation at the time the invention was made simply runs contrary to the clear teachings of the prior art references
In contrast to applicant's continaul assertions, the prior art did not limit the use of busulfan to cancer patients alone.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

For example, in contrast to applicant's continual assertions that Andersson et al. U.S. Patent Nos. 5,430,057 and 5,559,148 are directed to the treatment of neoplasms and fail to teach the use of bulsulfan together with other agents for facilitating hemopoietic chimerism,

Applicant still appears to ignore their own acknowledgement on pages 26-27 of the instant specification, which includes the citation of Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148; see entire documents) that methods of administering busulfan in therapeutic regimens were known and practiced at the time the invention was made.

Further, it has been noted that the Background of the Invention of Andersson et al.'s Patents clearly describe the well known use of busulfan in hemopoietic autologous and allogeneic transplantation as well as its advantages at the time the invention was made (also, see Summary of the Invention and Detailed Descriptin of the Preferred Embodiments).

Also, in contrast to applicant's continual assertions concerning effective dosages, the specification as-filed (e.g. see page 27, paragraph 2) is consistent with the prior art in that "the amount of aklylating agent and T cell depleted bone marrow may be determine by routine experimentation and optimized empirically" and discloses dosages consistent with the prior art.

Applicant's arguments are not consistent with the disclosure of the instant application as filed as well as with the teachings of the prior art, including references relied or disclosed in the application as-filed.

Therefore, one of ordinary skill in the art would have been motivated to administer busulfan at various times, including the claimed timing (e.g. see claims 30-32) to create hemopoietic space for T cell depleted bone marrow / stem cells as well as to optimize bioavailability.

Applicant's continual reliance upon the unexpected advantages of combining bulsulfan with costimulation blockade by relying upon the Exhibits of Kean et al., Guo et al. and Sirasugi et al. have not been found convincing in light of the clear teachings of the prior art in combining the claimed elements of bone marrow cells, hemopoietic space agents, including bulsulfan as well as CD40L:CD40 and CD28:B7 antagonists in tissue and organ transplantation.

Again as pointed out previously repeatedly, Sykes teach methods inducing specific nonresponsiveness or tolerance to various antigens by inducing hemopoietic chimerism, including transplant antigens by administering
T cell depleted bone marrow cells / stem cells (e.g. see columns 6-7; column 8, lines 53-55; columns 9-11, column 15, paragraph 1) (note: stem cells read on T cell depleted bone marrow cells);
hemopoietic space agents, including busulfan (e.g. see column 8, paragraph 1);,
CD40L-CD40 inhibitors, including antibodies that bind CD40 and
CD28-B7 inhibitors, including CTLA4Ig (e.g. see column 8, line 65 - column, line 36; column 12)
as it relates to tissue and organ transplantation (see entire document, including Summary of the Invention; Detailed Description; Claims).

In addition, Sykes describes numerous modes of administration of providing the above-mentioned elements of therapeutic regimen in combination before, concurrently and subsequent to transplantation (see Summary of the Invention and Detailed Description).

Administering bone marrow stem cells, including repeated administration of said cells prior to, during and after the transplant are described (see Summary of the Invention, including column 2, line 60 – column 3, line 49; and Detailed Description, including column 6, line 38 – column 7, line 46; columns 9 – 10)

While Sykes differs from the claimed methods by not disclosing the particular timing of busulfan in the claimed therapeutic methods to promote graft survival (e.g. see claims 30-32),
applicant's continual assertions that the prior art teachings does not provide for the various elements employed in promoting long term transplant survival ignores the clear teachings of the prior art.

In this case, the teachings of the prior art pertaining to the difficulties in achieving long term transplant survival and in the success in combining different immunosuppressive regimens to solve similar problems as applicant's invention would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144

The following previously newly added references were provided to make it clear that the prior art recognized the combination of immunosuppressive therapies addressing different targets to increase the desired immunosuppressive effect and to decrease the toxicity of each immunosuppressive in such regimens.

Strom et al. teach that it was known and practiced by the ordinary artisan to employ a multitiered approach to immunosuppressive therapy similar in principle to that used in chemotherapy, several agents are used simultaneously, each of which is directed to a different molecular target with the allograft response. Additive-synergistic effects are achieved through application of each agent at relatively low dose, thereby limiting the toxicity of each individual agent while increasing the total immunosuppressive effect (see entire document, including the introduction on page 451).

Sykes et al. also teach the advantages of mixed chimerism in employing immunosuppressive regimens associated with hemopoietic cell transplantation in the induction of central T cell tolerance for clinical use (see entire document, including Abstract and the last paragraph on page 786).

Wekerle et al. also teach the advantages of employing inhibitors of costimulation and CD40:CD40 ligand interactions that lead to chimerism in approaches to induce tolerance and overcome the problems of chronic organ graft rejection and immunosuppression-related toxicity (See entire document, including Abstract, Introduction and Discussion).

In contrast to applicant's continual assertions of insufficient teachings in the prior art or unexpected advantages, the prior art provides for the combination therapy encompassed by the claimed methods for the same or nearly the same reasons, that is, to achieve long term graft survival and reducing immunosuppression-related toxicities by combining inhibitors of B7:CD28:CTLA4 and CD40:CD40L pathways with standard or current immunosuppression regimens at the time the invention was made with an expectation of success in achieving said goals.

Again, the following of record is provided for applicant's convenience addresses applicant's arguments of record and those reiterated in applicant's amendment, filed 12/18/06.

While applicant continually argues that Sykes does not expressly disclose that administering busulfan in amounts that facilitates mixed hemopoietic chimerism, one cannot separate a product from its properties. Further, in this case, applicant acknowledges the use of busulfan to create hemopoietic space, therefore the effective amount of busulfan taught by the prior art does inherently facilitate hemopoietic chimerism.

With respect to the use an alkylating agent such as cyclophosphamide as an immunosuppressive agent, which can be administered subsequent to the administering T cell depleted bone marrow cells to a subject in a transplantation regimen, the following is noted.
The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 describes the known use of immunosuppressive drugs such as the aklylating agent cyclophosphamide in after transplantation and during rejection crises as well as maintenance regimens with relatively small doses of immunosuppressants (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide).

Shichi et al. (U.S. Patent No. 4,843,092) similarly teach the known use of immunosuppressive agents such as the alkylating agent cyclophosphamide as agents for suppressing rejection which may occur after transplantation of human organs (see column 1, second paragraph of Background Art).

Therefore, one of ordinary skill in the art would have administered the alkylating agent cyclophosphamide at various times prior to, during and subsequent to transplanting cells and tissues in order to provide the appropriate immunosuppressive environment to promote long term acceptance of transplants / grafts. It is clear that cyclophosphamide has been used for decades by the ordinary artisan in transplantation regimens.

Also, as indicated previously, the claimed timing and dosages of alkylating agents including busulfan or cyclophosphamide in the claimed therapeutic methods to inhibit rejection of transplant was obvious to one of ordinary skill in the art at the time the invention was made, as these limitations appear to be consistent with those employed in the prior art and with providing efficacy and bioavailability, while minimizing drug associated toxicities.

The following of record is provided for applicant's convenience addresses applicant's arguments of record and those reiterated in applicant's amendment, filed 3/27/06.

Sykes teach methods inducing specific nonresponsiveness or tolerance to various antigens by inducing hemopoietic chimerism, including transplant antigens by administering
T cell depleted bone marrow cells / stem cells (e.g. see columns 6-7; column 8, lines 53-55; columns 9-11, column 15, paragraph 1) (note: stem cells read on T cell depleted bone marrow cells);
hemopoietic space agents, including busulfan (e.g. see column 8, paragraph 1);,
CD40L-CD40 inhibitors, including antibodies that bind CD40 and
CD28-B7 inhibitors, including CTLA4Ig (e.g. see column 8, line 65 - column, line 36; column 12)
as it relates to tissue and organ transplantation (see entire document, including Summary of the Invention; Detailed Description; Claims).

In addition, Sykes describes numerous modes of administration of providing the above-mentioned elements of therapeutic regimen in combination before, concurrently and subsequent to transplantation (see Summary of the Invention and Detailed Description).

Administering bone marrow stem cells, including repeated administration of said cells prior to, during and after the transplant are described (see Summary of the Invention, including column 2, line 60 – column 3, line 49; and Detailed Description, including column 6, line 38 – column 7, line 46; columns 9 – 10)
Sykes differs from the claimed methods by not disclosing the particular timing of busulfan in the claimed therapeutic methods to promote graft survival (e.g. see claims 30-32). Claims 1-2 and 9-10 encompass the particular timing of busulfan administration encompassed by claims 30-32.

As acknowledged on pages 26-27 of the instant specification including the citation of Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148; see entire documents); modes of administering busulfan were known at the time the invention was made. Therefore, one of ordinary skill in the art would have been motivated to administer busulfan at various times, including the claimed timing (e.g. see claims 30-32) to create hemopoietic space for T cell depleted bone marrow / stem cells as well as to optimize bioavailability.

Slattery et al. teach that busulfan is an alkylating agents commonly used to ablate marrow before hemopoietic stem cell transplantation and the importance of analytical and pharmacokinetic aspects of therapeutic monitoring (see entire document, including the Summary on page 543). It is noted that the patients received bulsulfan doses every 6 hours over a period of 4 days (see Busulfan Concentration and Outcome of Transplantation).

Similarly Hassan et al. teach the known use of busulfan in myeloablative therapy in bone marrow transplantation and the importance of drug monitoring and individual dose adjustment in providing for busulfan bioavailability while reducing / avoiding drug-related toxicities (See entire document, including the Abstract).

Therefore, the claimed timing of busulfan in the claimed therapeutic methods to inhibit rejection of transplant was obvious to one of ordinary skill in the art at the time the invention was made, as these limitations appear to be consistent with those employed in the prior art and with providing busulfan efficacy and bioavailability, while minimizing drug associated toxicities.

Given the general applicability and desirability of the modes of inducing immunological nonresponsiveness to a variety of antigens, including a wide variety of cells, tissues and organs of interest, one of ordinary skill in the art would have been motivated to include the well known transplantation of skin grafts to the transplantation regimens taught by Sykes.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive

10. Claims 1, 9 and 33 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513)
in view of art known practice and modes of administration of alkylating agents
such as bulsulfan / cyclophosphamide at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. Therapeutic Drug Monitoring 20: 543-549, 1998) and Hassan et al. (Blood 84: 2144-2150, 1994), The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide) and Shichi et al. (U.S. Patent No. 4,843,092), Strom et al. (in Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, 1996; see pages 451-456), Sykes et al. (Nature Medicine 3: 783-787, 1997) and Wekerle et al. (J. Exp. Med. 187: 2037-2044, 1998)
and further in view of
Reinherz et al. (U.S. Patent No. 4,443,427), Tomita et al. (J. Immunol. 164: 34-41, 2000) (1449; Exhibit #274), Bingaman et al., Transplantation 69: 2491-2496 (2000) (1449; Exhibit 193), Larsen et al., Current Opinion in Immunology 9: 641-647 (1449; Exhibit 188), and Schaub et al., Journal of Allergy and Clinical Immunology 99: 5206, Abstract 843 (1997) (1449; #264) and in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449, Exhibit 225)
essentially for the reasons of record.

With respect to applicant's assertions filed 12/28/2007 in the Appeal Brief concerning the obviousness of the instant claims have been fully considered but have not been found convincing essentially for the reasons of record.

In addition to the newly added references above,
applicant's arguments and the examiner's rebuttal concerning the obviousness of the instant claims are essentially the same of record and reiterated herein for applicant's convenience.

Applicant's arguments have not been found persuasive.

The following is reiterated for applicant's convenience.

The teachings are set forth above.

As indicated previously, Sykes differs from the claimed methods by not disclosing "skin" per se as the tissue of organ of interest for transplantation. Claims 1 and 9 encompass skin grafts as the tissue / organ transplant of the claimed methods

Larsen et al. teach modes of inhibiting immune responses, including rejection of various tissues and organs including skin (e.g. see column 2; column 6, paragraph 4) by blocking CD40:CD40L and CTLA4:CD28:B7 pathways in order to induce immunological unresponsiveness in the transplant recipient (see entire document, including Background of the Invention, Summary of the Invention, Detailed Description and Claims).

Given the general applicability and desirability of the modes of inducing immunological nonresponsiveness to a variety of antigens, including a wide variety of cells, tissues and organs of interest, as taught by Sykes and Larsen et al.,one of ordinary skill in the art would have been motivated to include the well known transplantation of skin grafts to the transplantation regimens taught by Sykes, given the evidence by Larsen et al. that skin is among a list of known tissues that were routinely transplanted at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

11. Claims 1, 5, 6, 9-10, 12-23, 30, 34, 36-37, 44-52, 54-60, 62-63 and newly added claims 64-74 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Sykes (U.S. Patent No. 6,514,513)

in view of art known practice and modes of administration of alkylating agents such as bulsulfan / cyclosphophamide at various times to meet the needs of the patient, as acknowledged on pages 26-27 of the instant specification and as evidenced by Andersson et al. (U.S. Patent Nos. 5,430,057 and 5,559,148) (1449, Exhibits 2 and 4), Slattery et al. Therapeutic Drug Monitoring 20: 543-549, 1998) and Hassan et al. (Blood 84: 2144-2150, 1994), The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, edited by Beers et al., Merck Research Laboratories, Whitehouse Station, NJ, 1999 (see pages 1067-1074; particularly page 1072; Immunosuppression, Cyclophosphamide) and Shichi et al. (U.S. Patent No. 4,843,092), Strom et al. (in Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, 1996; see pages 451-456), Sykes et al. (Nature Medicine 3: 783-787, 1997) and Wekerle et al. (J. Exp. Med. 187: 2037-2044, 1998)

and in further view of Reinherz et al. (U.S. Patent No. 4,443,427), Tomita et al. (J. Immunol. 164: 34-41, 2000) (1449; Exhibit #274), Bingaman et al., Transplantation 69: 2491-2496 (2000) (1449; Exhibit 193), Larsen et al., Current Opinion in Immunology 9: 641-647 (1449; Exhibit 188), and Schaub et al., Journal of Allergy and Clinical Immunology 99: 5206, Abstract 843 (1997) (1449; #264)

and in view of Peach et al. (US 20020182211) essentially for the reasons of record.

With respect to applicant's assertions filed 12/28/2007 in the Appeal Brief concerning the obviousness of the instant claims have been fully considered but have not been found convincing essentially for the reasons of record.

In addition to the newly added references above,
applicant's arguments and the examiner's rebuttal concerning the obviousness of the instant claims are essentially the same of record and reiterated herein for applicant's convenience.

Applicant's arguments and the examiner's rebuttal are essentially the same as addressed above.

Applicant's arguments have not been found persuasive.

The teachings are set forth above.

The following is reiterated for applicant's convenience.

Sykes differs from the claimed methods by not disclosing the particular mutant CTLA4 mutant molecules, including L104EA29Yig CTLA4 recited in the instant claims as the inhibitory CTLA4 of the claimed invention, including the soluble CTLA4 mutants of newly added claims 65-74.

Peach et al. teach soluble CTLA4 mutant molecules, including the specific L104EA29YIg, which have greater avidity than CTLA4 and can bind either of CD80, CD86 or both (e.g., see Summary of the Invention) in immunomodulating regimens for the treatment or prevention of acute or chronic graft rejection, including in combination therapy (e.g. see paragraphs [0079] – [0084] on pages 8-9). The claimed extracellular domains as well as the claimed sequences (e.g. claims 44-52 and 56) are intrinsic properties of the referenced CTLA4 mutant molecules, including the specific L104EA29YIg taught by Peach et al.

Given the greater avidity soluble CTLA4 mutant molecules, including the specific L104EA29YIg, which can bind either of CD80, CD86 or both, one of ordinary skill in the art would have been motivated to substitute said soluble CTLA4 mutant molecules taught by Peach et al. in the referenced transplantation regimens taught by Sykes, in an effort to increase the efficacy of CTLA4 molecules to inhibit the desired CTLA4-mediated responses in promoting long term graft survival at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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